# CHEMOTHERTAPY INDUCED NEUROPATHY – PREVENTION AND MANAGEMENT

## INTRODUCTION

Cancer is the second leading cause of mortality worldwide, after only heart disease, and despite enormous efforts to introduce novel chemotherapy treatments, the condition continues to be of great concern on a global scale (Bray et al., 2018). According to Torre et al. (2015), there were 8.2 million cancer deaths and 14.1 million new cases of the disease worldwide in 2012. The International Agency for Research on Cancer (IARC) predicted that there were 18.1 million new cases of cancer in 2018, followed by 9.6 million deaths (Bray et al., 2018). Ageing of the population, changes in reproductive variables, and bad lifestyle choices all contribute to the rising incidence and mortality of cancer.

The three main cancer treatments are surgery, chemotherapy, and radiation therapy; however, each of these approaches carries a significant risk of adverse effects[1].

Cancer has been treated with chemotherapeutic drugs for the last fifty years. Chemotherapy is a drug treatment involving chemicals that are poisonous (cytotoxic) cancerous cells. The chemotherapeutic agents disrupt the cell division process by damaging the control centre of the cell, such as proteins or DNA. Chemotherapy uses chemicals to treat cancer, and is particularly appropriate for cancers that have metastasised and cannot be treated any longer by contained methods such as surgery and radiation. Chemotherapy has long been one of the most important parts of cancer treatment. The main aims of chemotherapy vary, and can range from intention-to cure to provision of comfort (i.e., palliation)[2].

There are two types of chemotherapy: neo adjuvant chemotherapy and adjuvant chemotherapy. Neo adjuvant chemotherapy is administered before surgery allowing the possibility of shrinking the tumour before surgery or seeing how the tumour responds to the chemo drugs. Adjuvant chemotherapy is administered after surgery to kill any remaining cancer cells that cannot be seen.

Neo-adjuvant chemotherapy is used to reduce the size of a tumour prior to surgery and also to prevent development of micro-metastasis. Neo-adjuvant chemotherapy is being increasingly utilized in patients with locally advanced breast cancer and many centres are favouring treatment with cytotoxic agents and radiotherapy before surgery to “downstage” tumours, opening the possibility of limited surgery such as lumpectomy and thus to avoid mastectomy.

Adjuvant chemotherapy is given after surgery to reduce the risk of recurrence and to eliminate micro-metastasis thereby preventing distant metastasis[3].

## SIDE EFFECTS OF CHEMOTHERAPY

Common side effects of chemotherapy include Chemotherapy induced peripheral Neuropathy (CIPN), fatigue, nausea, diarrhoea, mouth sores, hair loss, anaemia and changes in blood cell counts. These adverse effects not only contribute to physical discomfort but also significantly impact the emotional and psychological well-being of patients. Thus, exploring effective complementary interventions to alleviate these symptoms is crucial in enhancing the overall quality of life for individuals undergoing chemotherapy. Chemotherapy side effects are many which need special attention. It calls for some sort of complementary therapy.

A portion of the chemotherapeutic drugs for malignancy treatment can harm fringe nerves. At the point when this occurs because of chemotherapeutic operators then it is called Chemotherapy Induced Peripheral Neuropathy (CIPN) (ASCO, The American Society of Clinical Oncology 2016).

## CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY (CIPN)

The problem of chemotherapy-induced peripheral neuropathy (CIPN), which can be caused by potentially neurotoxic chemotherapy, is becoming more and more important in oncological treatments that aim to cure and treat cancer. When acute CIPN develops during chemotherapy, the dose may need to be lowered or stopped, which might have a negative effect on survival. After completing chemotherapy, over 30% of patients would still have CIPN after a year or more after finishing chemotherapy[4].

Approximately 60% of men and women undergoing chemotherapy treatment for breast cancer will develop CIPN (Piccolo & Kolesar, 2014). A problem faced by many breast cancer survivors is poor CIPN treatment coupled with practitioners' lack of understanding about their subsequent quality of life (QOL; Bakitas, 2007; Miltenburg & Boogerd, 2014).

Lack of a "gold standard" assessment tools, conflicting utilization of terms, less of mental science proof to help the use of self-report instruments in malignancy populations, and absence of multidimensional attributes are some of the confinements related to CIPN **(Dunlap & Paice, 2006)**. Complete assessment of CIPN is an essential step for the improvement of medical interventions to advance well-being, alleviate symptoms, and expand personal satisfaction for people with malignant growth.

Clinical evaluation of malignancy-related neuropathic pain represents some significant difficulties analytically extra as in forming a reasonable and dependable last evaluation in controlled clinical preliminaries.

Peripheral neuropathy, which affects almost all oxaliplatin patients, can cause sensory abnormalities such allodynia, paraesthesia, and neuropathic pain as well as tingling and numbness in the stocking-glove distribution. Peripheral neuropathic pain, which can feel scorching, shooting (like an electric shock), cramping, tingling, itching, hot, or cold, is a common side effect for patients using oxaliplatin[5]. Peripheral neuropathic pain can reduce or even cease the effectiveness of treatment, which raises the risk of cancer recurrence. Peripheral neuropathic pain can impair function, have a negative effect on sleep, diminish quality of life, and exhaust the sufferer.

**MECHANISMS OF CINP:**

The exact mechanisms underlying chemotherapy-induced neuropathy are complex and can vary depending on the specific chemotherapy drugs used. However, some general mechanisms and contributing factors have been identified:

**Mitochondrial Dysfunction**: Some chemotherapy medications can impair the mitochondrial process in nerve cells. When mitochondria are damaged, nerve cells may not function properly, resulting in neuropathy. Mitochondria are in charge of generating energy (ATP) for the cell.

**Axonopathy:** The long nerve cell projections known as axons, which are in charge of delivering electrical signals, can be directly harmed by chemotherapy medications. Due to this damage, normal nerve signal transmission may be disrupted, resulting in sensory and motor abnormalities.

**Apoptosis and Cell Death:** Chemotherapy-related nerve injury can cause nerve cells to undergo programmed cell death (apoptosis). This might lead to the death of working neurons, which would exacerbate neuropathic symptoms.

**Inflammation:** Chemotherapy can cause the nervous system to become inflamed. Inflammatory chemicals can impair the regular operation of nerve cells, which aggravates pain and other neuropathic symptoms.

**Oxidative Stress:** Reactive oxygen species (ROS) are produced more frequently by chemotherapy medicines, which causes oxidative stress. ROS can harm and impair the function of nerve cells.

**Ion channel disruption:** Chemotherapy medications can impact the ion channels in nerve cells, which can result in aberrant nerve signalling. Sensory abnormalities including tingling and numbness may result from this.

**Chemical Neurotransmitter Alteration:** The neurotransmitter equilibrium in the nervous system may be affected by several chemotherapy medications. Changes in neurotransmitter levels can worsen neuropathic symptoms by impairing normal nerve signalling.

**Chemotherapy-induced artery damage** : may lead to a reduction in the supply of oxygen and nutrients to nerve cells, which may contribute to nerve dysfunction.

**Genetic sensitivity:** Genetic factors may have an impact on a person's susceptibility to chemotherapy-induced neuropathy. It's likely that certain genetic variations make certain people more vulnerable to nerve damage.

It's significant to remember that various chemotherapy medications have unique methods of action and may affect nerve cells in various ways. Additionally, a patient's genetic makeup and general health status may have an impact on the severity and progression of chemotherapy-induced neuropathy.

The complexity of chemotherapy-induced neuropathy emphasises the need for additional study to comprehend its causes and create efficient management and prevention plans. Finding biomarkers and potential treatment targets to lessen the negative effects of chemotherapy-induced neuropathy on the quality of life of cancer patients has been increasingly important in recent years.

## RISK FACTORS FOR CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Common and potentially crippling, chemotherapy-induced neuropathy (CINP) is a side effect of cancer treatment. For early intervention and individualised patient care, it is critical to recognise the risk factors and anticipate the emergence of CINP. **The following are some of the main CINP risk factors and warning signs:**

**Drugs used in chemotherapy** The possibility for neuropathy to be caused by various chemotherapy medications varies. The risk of generating CINP is known to be increased with

platinum-based medications (like cisplatin), taxanes (like paclitaxel), vinca alkaloids (like vincristine), and proteasome inhibitors (like bortezomib).

**The cumulative dose of chemotherapy** a patient has had as a whole can affect their likelihood of developing CINP. Over the course of treatment, higher cumulative doses may raise the risk of experiencing neuropathic symptoms.

**Length of Treatment**: Multiple chemotherapy rounds and longer treatment times may have an impact on the development of CINP.

**Individual susceptibility**: Genetic factors can affect a person's susceptibility to CINP. Genetic alterations in the genes linked to inflammation, nerve function, and drug metabolism may affect the probability of developing neuropathy. Patients who already suffer from neuropathy, diabetes, autoimmune illnesses, or other neurological issues may be more susceptible to CINP.

**Standard neurological condition**: The risk that a patient may develop CINP after treatment can be influenced by their neurological condition at baseline.

**Genetic sensitivity**: Genetic factors may have an impact on a person's susceptibility to chemotherapy-induced neuropathy. It's likely that certain genetic variations make certain people more vulnerable to nerve damage.

**Preexisting Neuropathy:** Chemotherapy-induced neuropathy may be more likely to affect patients who already have neuropathy or other neurological problems.

**Age and Sexes:** In several studies, being a woman and being older have been linked to a higher chance of getting CIN.

**FORECASTING OF CHEMOTHERAPY-INDUCED NEUROPATHY (CINP)**

**Clinical Evaluation:** Regular clinical evaluations that include physical exams and patient-reported symptoms can aid in predicting and monitoring the emergence of CINP. Baseline evaluations offer a point of reference.

**Nerve conduction studies (NCS) and electromyography (EMG)** are two neurophysiological tests that can assess nerve function and help predict CINP. Neuropathy may be indicated by changes in the characteristics of nerve conduction.

Measurements of a patient's response to numerous sensory stimuli are made during quantitative sensory testing (QST). Sensory perception changes may be the first symptom of CINP.

Researchers are looking into possible **biomarkers** that could be found in blood, cerebrospinal fluid, or other biological samples and potentially foretell the emergence of CINP.

**Genetic Markers:** Genetic testing and the detection of particular genetic variations can be used to forecast a person's propensity to CINP.

**Machine Learning:** Using a mix of patient features, treatment regimens, and genetic data, it is possible to predict CINP using advanced computational techniques, such as machine learning algorithms.

**Patient-Reported Outcomes:** Information regarding symptoms and quality of life provided by patients may provide insight into how CINP manifests.

**Early Symptoms:** Early neuropathy symptoms can be identified while undergoing treatment and can help predict how CINP will progress.

Healthcare professionals can apply preventive measures and interventions to control symptoms by identifying patients who are more likely to develop CINP. This could potentially improve patient wellbeing and treatment outcomes.

**PREVENTION OF CHEMOTHERAPY-INDUCED NEUROPATHY:**

**The prevention of chemotherapy-induced neuropathic pain (CINP)** is a difficult but crucial objective in the treatment of cancer. There are a number of tactics that can help lessen the risk and severity of CINP, even if complete prevention may not always be possible. The following are some investigated preventative tactics:

**Modification of the dose schedule:**

Modifying the chemotherapy regimen or timetable to reduce nerve damage while preserving treatment efficacy. The effect on nerves can be lessened by using smaller doses or spacing out doses over longer periods of time. Chemotherapy, a treatment that makes use of medicines that can protect nerve cells from the damage that chemotherapy causes.

A little amount of neuroprotection may be offered by **antioxidants** and drugs like amifostine.

**Combination therapy** is combining chemotherapy with medications that slow down or hasten the healing of injured nerves. This method reduces the negative effects of chemotherapy on nerve function.

**Vitamin Supplementation:** Studies have been done on the capacity of certain vitamins, such as vitamin E, vitamin B12, and alpha-lipoic acid, to prevent or lessen CINP.

**Supplementing with glutamine:** According to some research, taking oral glutamine supplements may help avoid or lessen the neuropathy brought on by some chemotherapy drugs.

**Patient education** can encourage patients to take action by teaching them about the neuropathy symptoms and indicators, the value of early detection, and self-care techniques.

**Multidisciplinary Care:** The effectiveness of prevention and management techniques can be improved by working together with a multidisciplinary healthcare team that includes neurologists, oncologists, and pain experts**.**

**Acupressure and acupuncture** are complementary therapies that have been researched for their ability to treat neuropathic symptoms.

**Pharmacogenomics:** By customising chemotherapy regimens based on patient genetic profiles, genetic testing may help patients' susceptibility to CINP.

**Physical activity and rehabilitation:** Regular exercise and physical treatment can support the maintenance of nerve health and function.

**Cryotherapy:** Cooling the extremities while receiving chemotherapy to constrict blood arteries and lessen nerve exposure to the medication. Studies on cold socks and gloves for patients receiving particular chemotherapy medications have been conducted.

**Dealing with Risk Factors:** Reduced susceptibility to CINP can be achieved by identifying and treating patient-specific risk factors, such as underlying diseases or preexisting neuropathy.

**Meditation** and other mindfulness practises, as well as relaxation drills, can help control neuropathic pain and enhance general wellbeing.

**Clinical Trials:** Taking part in studies looking at ways to prevent CINP will help advance knowledge and uncover better prevention tactics.

It's crucial to remember that the efficiency of these prophylactic measures can change depending on the features of each patient, the particular chemotherapy drugs employed, and the initial cancer diagnosis. The risks and advantages of proposed preventative measures should be discussed openly between patients and healthcare professionals while keeping the whole treatment plan in mind.

## MANAGEMENT OF CHEMOTHERAPY INDUCED NEUROPATHY

A comprehensive strategy that includes both pharmaceutical and non-pharmacological therapies is necessary to manage chemotherapy-induced neuropathic pain (CINP). The

objective is to reduce suffering, raise quality of life, and improve the general health of cancer patients. The following are some tactics for controlling CINP:

**Pharmacy management:**

**Analgesic Drugs**

Acetaminophen and nonsteroidal anti-inflammatory medications (NSAIDs), which are non-opioid analgesics, can help control mild to moderate pain.

For more severe pain, opioid drugs may be explored, but careful monitoring is required to avoid addiction and side effects.

**Antidepressants**

Selective serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, and tricyclic antidepressants (such as amitriptyline and nortriptyline), have demonstrated efficacy in the treatment of neuropathic pain.

**Anticonvulsants**

Pregabalin and gabapentin are two drugs that are frequently prescribed to treat neuropathic pain. They can lessen pain signals and ameliorate symptoms brought on by nerves.

**Medications for the Skin**

Lidocaine creams or patches can relieve neuropathic pain locally. When administered to the sore area, capsaicin cream—a compound derived from chilli peppers—can also be beneficial.

**Narcotic painkiller**

Opioid drugs may be provided in cases of extreme neuropathic pain while being closely monitored by a doctor.

**NON-PHARMACOLOGICAL MANAGEMENT**

**Physical Exercise**

Physical therapy and targeted exercises can help maintain joint mobility, increase muscular strength, and reduce pain.

**Workplace Therapy**

To enhance daily functioning and lessen pain, occupational therapists might suggest assistive devices and teach adaptive skills.

**TENS** is short for transcutaneous electrical nerve stimulation. TENS uses light electrical currents to be applied to the skin, which can block pain signals and offer comfort.

**Acupuncture therapy and acupressure**

These conventional treatments encourage relaxation and stimulate particular body locations, which may help reduce neuropathic pain.

**Techniques for Meditation and Relaxation**

Deep breathing, meditation, and progressive muscle relaxation are all methods that can be used to manage pain and lessen stress.

**Psychological assistance**

Patients can learn coping mechanisms and learn to control the emotional effects of pain with the use of cognitive-behavioral therapy (CBT) and counselling.

**Nutritional Assistance**

A nutritious, well-balanced diet may promote overall health and support healthy nerve function.

**Additional Treatments**

Under medical supervision and with prudence, one may experiment with herbal supplements, dietary modifications, and other complementary therapies.

Patient Education Patients can take an active role in their own pain management by being informed about their disease, available resources, and pain management approaches.

**Support Teams**

Joining support groups or getting in touch with people who have gone through similar suffering can offer both emotional support and useful guidance.

Individualised management solutions should be chosen based on the patient's unique requirements, preferences, and medical background. A multidisciplinary approach to healthcare that includes experts from numerous fields.

## EMERGING THERAPIES OF CINP

Chemotherapy-induced neuropathic pain (CINP) is a tough condition that is continually evolving as a result of ongoing research into new treatments and better ways to manage it.

Here are some potential future directions and cutting-edge CINP prevention and treatment approaches.

**1.Personalised Drug Delivery**

The creation of targeted drug delivery devices that administer painkillers directly to the nerves that are being damaged while reducing systemic adverse effects.

To improve therapeutic outcomes, local drug administration techniques and nanoparticle-based strategies are being investigated.

**2.Modulation of Neuroinflammation**

Examining treatments that take neuroinflammation, a major cause of neuropathic pain, into consideration. Anti-inflammatory medications and immune-modulating substances may present fresh paths for intervention.

**3. Neurotrophic Factors**

Investigating the use of nerve growth factors to encourage nerve regeneration and repair.

4. **Modulators for Ion Channels**

developing medicines that specifically target the ion channels that are involved in the signalling of neuropathic pain in an effort to prevent pain transmission without impairing normal nerve function.

**5.The use of epigenetic therapies**

examining epigenetic alterations as potential CINP treatment targets.

Epigenetic therapies may modify gene expression and change how the nervous system reacts to the harm caused by chemotherapy.

6.**Microbiome Interventions**

investigating how the gut microbiome affects how sensitively nerves respond to neuropathic pain and how well they function. It is being investigated whether probiotics, prebiotics, and other microbiome-focused therapies can lessen CINP.

**7.Gene Therapy**

delivering therapeutic genes directly to injured neurons using gene therapy techniques to encourage repair and lessen discomfort.

The possibility of using viral vectors and other gene delivery techniques to treat CINP is being researched.

**8.Stem cell treatments**

investigating the use of stem cells in CINP to regenerate and repair injured nerves.

As prospective treatments, stem cell transplantation and tissue engineering techniques are being investigated.

**9.Techniques for Neuromodulation**

new methods for treating neuropathic pain, including spinal cord stimulation, transcranial magnetic stimulation (TMS), and peripheral nerve stimulation.

For targeted pain management, non-invasive neuromodulation techniques are being improved.

**10. Individualised Healthcare**

creating biomarkers and prediction models to identify individuals who are more likely to develop CINP, as well as developing treatment strategies that are specific to each patient's needs. Pharmacogenomics and individualised pain management techniques might advance.

**11. Multiple Therapies**

investigating the benefits of combining several treatments, such as prescription drugs, physical therapy, and complementary methods, for better pain management.

While these novel therapeutics show promise, more investigation, preclinical research, and clinical trials are required to confirm their efficacy and safety in the prevention and management of chemotherapy-induced neuropathic pain. Novel therapy strategies are likely to develop as our knowledge of the underlying mechanisms of CINP expands, giving patients suffering from this difficult condition fresh hope.

**The management of chemotherapy-induced neuropathic pain (CINP) is governed by a number of clinical guidelines and recommendations.**

**GUIDELINES AND RECOMMENDATIONS**

**American Society of Clinical Oncology (ASCO)**

Guidelines for the treatment of peripheral neuropathy brought on by chemotherapy have been released by ASCO. These recommendations address the prevention, detection, and treatment of neuropathy in chemotherapy-treated cancer patients.

**European Society for Medical Oncology (ESMO)**

ESMO has offered advice for doctors on monitoring, assessment, and intervention with regard to the prevention and management of chemotherapy-induced neuropathy.

National Comprehensive Cancer Network (NCCN) . The NCCN Clinical Practise Guidelines in Oncology include thorough information on cancer treatment, including suggestions for treating peripheral neuropathy brought on by chemotherapy. These recommendations cover methods for diagnosing and managing neuropathy based on the particular chemotherapy drugs utilised.

**American Pain Society (APS) Clinical Practice Guidelines**

Clinical practise recommendations for the treatment of neuropathic pain were released by the APS. These guidelines include basic guidelines and suggestions for treating neuropathic pain, which can be used to CINP therapy even if they are not particular to CINP utilised chemotherapeutic drugs.

**Canadian Pain Society (CPS) Guidelines**

For the pharmaceutical therapy of neuropathic pain, CPS has developed guidelines. These recommendations could provide information on pharmacological methods for treating CINP.

**International Association for the Study of Pain (IASP)**

The IASP offers tools and recommendations for managing pain, particularly neuropathic pain. Their suggestions may contribute to a deeper comprehension of the treatment of neuropathic pain.

**Organisational Regulations** Based on their patient populations and available resources, many cancer treatment facilities and institutions may create their own standards and protocols for addressing CINP.

The needs, medical history, and particular chemotherapy regimen of each patient should be taken into account when applying clinical guidelines. To make sure that the chosen interventions fit with the patient's preferences and goals, guidelines should be adjusted to the patient's circumstances and healthcare providers should participate in shared decision-making with the patient.

Consult the most recent versions of the guidelines from reliable sources like ASCO, ESMO, NCCN, and other pain management organisations for the most current and complete advice.

## CONCLUSION

During cancer treatment, chemotherapy-induced neuropathic pain (CINP) is a serious and frequently difficult consequence that can occur. Prevention, early detection, and efficient management are crucial for this debilitating disorder because of the significant impact it can have on patients' quality of life. Our methods for preventing and treating CINP are constantly changing along with our understanding of its underlying causes.

The prevention of CINP involves a variety of tactics, such as dose adjustment, tailored drug administration, and research into neuroprotective drugs and genetic indicators. These methods seek to lessen nerve damage and increase patients' tolerance to chemotherapy while lowering the possibility of developing neuropathic pain.

A comprehensive approach to care is crucial when prevention is not an option. Analgesics, antidepressants, and anticonvulsants are a few examples of the pharmacological treatments available.

## REFERENCES

1. Mhaske N. Assess the side effects and coping strategies adopted by cancer patients receiving radiation therapy. Indian Journal of Surgical Nursing 2013; 2:81-83. Available from www.researchgate.net › publication › 338401987. Cited on 12-3-2022 at 10am.

2. Lalla, Rajesh V., Stephen T. Sonis, and Douglas E. Peterson. Management of oral mucositis in patients who have cancer. Dental Clinics of North America.2008; 61-77. Available from www.dental.theclinics.com/article/S0011-8532(17)30097-6/ Cited on 16-4-2022 at 10am.

3. Cancer Research UK. Cancer statistics for the UK: incidence, mortality, survival, prevalence and lifetime risk. Cancer Research UK. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk. Published 2009. Accessed July 6, 2023

4. Lesley A Colvin Chemotherapy-induced peripheral neuropathy (CIPN): where are we now? PAIN: May 2019 - Volume 160 - Issue - p S1-S10 Author manuscript; available in PMC 2020 May 1. Cited on 22-3-2022 at 10pm doi: 10.1097/j.pain.0000000000001540

5. So Young Yoon and Jeeyoung Yo, Neuropathic cancer pain: prevalence, pathophysiology, and management, Korean J Intern Med. 2018 Nov; 33(6): 1058–1069, Published online 2018 Jun 25. Cited on 22-3-2022 at 8 pm doi: 10.3904/kjim.2018.162

---